REMARKS

Consideration and entry of this paper, and reconsideration and withdrawal of all rejections of the application, and allowance of the claims, especially in view of the remarks herein, are respectfully requested, as this paper places the application in condition for allowance, or in better condition for appeal.

Rejections under 35 U.S.C 103(a)

The only rejections outstanding are the rejections of claims 1-10 under 35 U.S.C 103(a), as summarized in points 6 and 7 of the Final Office Action. These rejections are respectfully traversed, as follows:

(A) Egholm in view of Vadarajan et al. and Kane et al.

Egholm involves PNA molecules. The Office Action alleges that the combination of Egholm with Vadarajan et al. and Kane et al. renders claims 1-9 obvious. Applicant's respectfully disagree.

The Final Office Action states:

> "*Vadarajan teaches that while it is possible to attach more than 10^3 boron atoms to an antibody molecule, such heavily boronated antibody conjugates suffer from significantly reduced immunoreactivity or tumor uptake*"

and also states that:

> "*Vadarajan further teaches that the hydrophilicity of these peptide structures may be markedly increased by using anionic [nido-7,8,$C_2B_9H_{11}$]$^-$ moieties*".

These statements are used to support the allegation that boronation increases the hydrophilicity of peptides, and it would therefore have been obvious and desirable to one of skill in the art to formulate the boronated PNA molecules of the present invention. However, these phrases of Vadarajan have been taken out of context. Vadarajan in fact teaches that the hydrophilicity of peptides that are **already** boronated can be increased by converting their hydrophobic closo-carborane groups to anionic nido-carboborane groups. When Vadarajan states that the hydrophilicity of peptide structures may be markedly increased, he is referring to peptide structures that are **already** boronated. Thus Vadarajan does not teach or suggest that

boronating a peptide increases its hydrophilicity. Instead he teaches that peptides with hydrophilic borane groups have a greater hydrophilicity than peptides with hydrophobic borane groups.

Furthermore, when read as a whole, Vadarajan **teaches away** from the proposition that boronating a molecule increases its hydrophilicity since it teaches that:

(a) boronated antibodies "*suffer from....low tumor uptake*" (see first paragraph of the introduction), and

(b) dipeptides that are already boronated have low solubility and can be converted to water soluble hydrophilic derivatives by performing cation exchange to form a sodium salt.

Vadarajan also **teaches away** from boronating molecules that have biological activity. Vadarajan teaches that boronated antibodies "*suffer from....reduced immunoreactivity*" and as a result are ineffective in binding to tumors. This is why Vadarajan chooses to switch from boronating the antibodies themselves, to boronating small dipeptides. These small dipeptides are not used to carry out any biological activity, such as binding to tumor cells. Instead these small didpeptides are simply attached to the antibodies. The antibodies "tagged" with **separate** boron-containing dipeptides thus retain their ability to bind to tumors.

Likewise, Kane et al. merely teaches overcoming the problems associated with incorporating boron into antibody molecules, by producing "*hydrophilic B-rich "trailer molecules*" which are simply "*attached to monoclonal IgG antibodies*". (See the first paragraph of Kane et al.).

Thus, neither Vadarajan nor Kane teach that a molecule having a biological activity can be boronated. Instead both Vadarajan and Kane teach away from this, as they show that boronating a molecule that has biological activity, such as an antibody, disrupts its function, and that instead small boron-rich dipeptide "tags" should be attached to the molecule.

In light of the above, one of skill in the art would have no motivation to boronate a PNA molecule, and would have no expectation that a boronated PNA molecule would retain its key biological activities of being able to penetrate the cell membrane, enter the nucleus, and subsequently bind to DNA or RNA. Prior to the present invention one of skill in the art would have had no expectation that a PNA molecule could be formulated to include carboborane groups without severely compromising these activities. This is especially true when one considers the difference in size between an antibody molecule and a PNA molecule. A single nucleotide has a

molecular weight in the order of 100s of Daltons – whereas antibodies are typically around 150 **Kilo** Daltons in size. Thus, one would expect that if boronating an antibody disrupts its biological function, surely boronating a much smaller PNA oligonucleotide would disrupt the ability of that PNA molecule to bind to DNA or RNA.

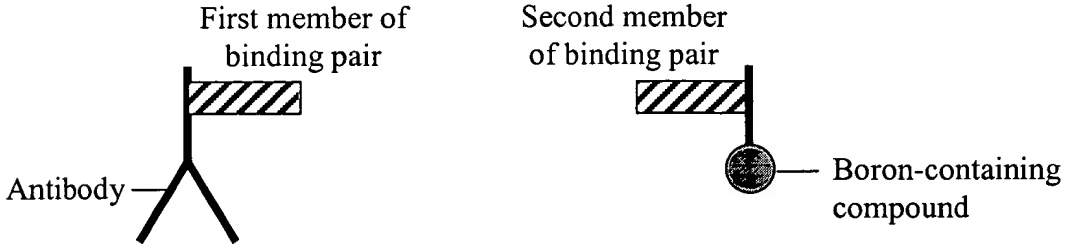
The present invention involves PNA molecules that are formulated to incorporate carboborane groups within their core structure, and which **surprisingly** retain their ability to penetrate the cell membrane and enter the nucleus. Data demonstrating the ability of the claimed PNAs to penetrate the cell membrane and enter the nucleus is provided in the Inventor's Declaration, which is submitted herewith in accordance with 37 C.F.R. §1.132.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C 103(a) over the combination of Egholm with Vadarajan et al. and Kane et al., is respectfully requested.

(B) Griffiths in view of Vadarajan et al.

The Office Action also alleges that claims 1-3, 5, and 10 are obvious under 35 U.S.C §103(a) over the combination of Griffiths and Vadarajan et al. Applicant's respectfully disagree.

The combination of Griffiths and Vadarajan also does not make it obvious to formulate the PNA molecules of the present invention, and does not provide any expectation that PNA molecules formulated to include carboborane groups would be successful or useful. Griffiths et al. teaches that adding boron groups to an antibody is undesirable because it disrupts its ability to bind to tumors (See Col 2 lines 51-52 and Col 2 line 67 to Col 3 line 4). The invention of Griffiths et al. purports to overcome this problem by (a) using an antibody to which a "first member of a binding pair" has been added, (b) binding this antibody to the tumor, and then (c) administering a boron-containing compound to which a "second member of a binding pair" has been added, as a result of which the boron-containing compound is targeted to the tumor. The strategy proposed by Griffiths et al. is illustrated below.



The only binding pairs that are exemplified in Griffiths et al. are biotin/avidin binding pairs. Although the specification does mention that pairs of complementary oliogonucleotides, such as PNAs, could be used as members of the binding pair, there is no demonstration that this would succeed. Furthermore, there is no teaching that the PNA molecules **themselves** should be formulated to incorporate boron-containing compounds. Instead the suggestion is only to "tag" one of the PNA molecules with a **separate** boron-containing compound.

Thus, Griffiths et al. provides no suggestion of using PNA molecules which themselves are formulated to incorporate boron-containing compounds. Furthermore, Griffiths provides no demonstration that either boron "tagged" PNA molecules or PNAs that are formulated to incorporate boron-containing compounds, would retain their ability to penetrate the cell membrane, enter the nucleus, and subsequently bind to DNA or RNA.

Thus, all of the cited art (including Griffiths) **teaches away** from the PNAs of the present invention. Furthermore, none of the cited references teach or suggest that carboborane groups can be incorporated into a PNA molecule. Instead the cited references teach that incorporating carborane groups into functional bio-molecules will disrupt their biological function.

In addition, numerous references in the art demonstrate that modifications to the structure of PNA molecules can result in a reduced DNA binding activity. See for example Mokhir et al. (enclosed) which shows that PNA molecules modified to contain dioxime ligands have reduced DNA binding affinity as compared to un-modified PNAs. See also Kehler et al. (enclosed) which shows that protected derivatives of PNA oligonucleotides have inferior DNA and RNA binding affinity as compared to un-modified PNAs.

Thus, one of skill in the art would not be motivated to incorporate carboborane groups into a PNA molecule, and would have no expectation that such modified PNA molecules would retain their key biological activities. The Examiner is respectfully reminded that "obvious to try" is not the legal standard by which an obviousness rejection should be based, and that instead there must be some expectation of success. The present invention involves PNA molecules that are formulated to incorporate carboborane groups within their core structure, and which **surprisingly** retain their ability to penetrate the cell membrane and enter the nucleus. Data demonstrating the ability of the claimed PNAs to penetrate the cell membrane and enter the nucleus is provided in the Inventor's Declaration submitted herewith in accordance with 37 C.F.R. §1.132.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C 103(a) as obvious over the combination of the combination of Griffiths and Vadarajan et al., is respectfully requested.

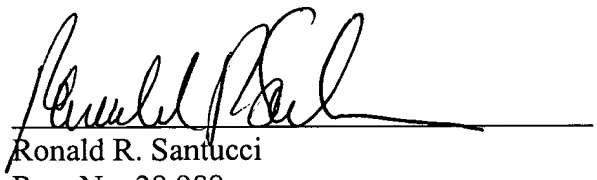
(C) Declaration under 37 C.F.R. §1.132

In support of the above arguments, the Examiner is kindly asked to review the Inventors Declaration, which is submitted herewith in accordance with 37 C.F.R. §1.132. This Declaration provides data demonstrating the **surprising** ability of the claimed PNAs to penetrate the cell membrane and enter the nucleus, and also contains arguments as to why the present claims are not obvious over the cited art.

CONCLUSION

In view of the remarks herein, and the Inventor's Declaration submitted herewith, the application is believed to be in condition for allowance, or in better condition for appeal. Entry of this paper, favorable reconsideration of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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